REMARKS

Claims

Claims 1–3, 5–8 and 10–15 are currently under examination with claims 4 and 9 cancelled without prejudice or disclaimer.

Claim amendments

Amended claim 1 recites the material elements (i.e., constituents) of the claimed combination(s). Support for the claim amendment can be found in, for example, paragraph [0024] of the published application.

Amended claim 5 is supported by, for example, the disclosure contained in paragraph [0024] of the published application (i.e., medicine *can* contain further additives).

Claim 7 has been amended to correct for a minor typographical error.

Claims 10 and 11 have been made dependent on claims 7 and 8, respectively. The amended claims comply with the requirements under §112, ¶4.

The amendment of claim 12 is self-explanatory.

It is respectfully submitted that the claim amendments do not raise new matter. Entry thereof is respectfully requested.

Claim objections

The Examiner is thanked for his careful review of the claims. The forgoing amendments render the objections moot. Withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §112

Applicants respectfully disagree with the PTO's contention that recitation of "pharmaceutical carrier" in the claims introduces new matter. Applicants' specification, for example, paragraph [0018] of the published application, explicitly teaches that the combinations of the present invention can be administered in "pharmacological forms." However, in order to expedite prosecution, the claims have been amended as per the Examiner's suggestion. No agreement is to be implied. Withdrawal of the rejection is respectfully requested.

Rejection under §103(a)

Claims 1–3, 5–8 and 10–15 are rejected under §103(a) as allegedly rendered obvious by Biewenga (*ABB*, 1994) in view of Mira (*Biochem. Pharmacol.*, 1994) further in view of Yeadon (US patent application publication No. 2004/0167153; *hereinafter* the '153 publication). This is a newly-

cited rejection. The Examiner alleges that it would have been *prima facie* obvious to combine Biewenga's disclosure on the use of α-lipoic acid against lung emphysema and Mira's disclosure of the use of silibinin as an antioxidant and HOCl scavenger to develop a composition comprising the two compounds using the methods disclosed by Yeadon. This contention is respectfully traversed.

Biewenga generically teaches efficacy of α-lipoic acid against lung emphysema. As conceded at page 4 of the Office Action, the primary reference "does not teach silibilin or inhalation." However, according to the Examiner, Silibilin is taught in Yeadon's '153 publication. The Office Action at page 4 further proceeds to contend that the motivation to combine the two agents can be obtained from Mira's teachings. Applicants respectfully disagree with this analysis.

Applicants respectfully submit that a combination of the cited references fails to *prima facie* render obvious the claims of the present application. Obviousness requires a suggestion of all the elements in a claim (*CFMT Inc., v Yieldup Int'l Corp.* 349 F.3d 1333, 1342 [68 USPQ2d 1940] (Fed. Cir. 2003)) and requires a reason that would have prompted [a skilled worker] to combine the elements in the way the claimed new invention does. *Ex parte Alexander* (86 USPQ2d 1120). Withdrawal of the rejection is respectfully requested. Nothing in the teachings of Biewenga, Mira or Yeadon provides a suggestion to combine the two classes of compounds (i.e., a free radical scavenger and an effector of glutathione metabolism). Moreover, neither Mira nor Yeadon give any advice for the treatment of COPD with the claimed agents.

The Office Action further contends that a skilled artisan would be motivated to use the aforementioned agents "in a combinatory therapy." See, the paragraph bridging pages 5 and 6 of the Office Action. The Office Action cites *In re Kerkhoven* 205 USPQ 1069(CCPA 1980) to contend that "The combination of compounds for a certain function where the compounds are known to have the function individually is *prima facie* obvious." At the outset, Applicants submit that this statement is incorrect. In *Kerkhoven*, the CAFC held that "It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose (emphasis added)." As such, the PTO's reliance on *In re Kerkhoven* in this particular case is legally misplaced.

It is respectfully submitted that the decision in *Kerkhoven* was made with respect to spray-dried detergent compositions comprising anionic and nonionic detergent materials, whereas the compositions of the instant invention comprise agents that are known in the art to have different biological targets and, as such, effects. Thus the compounds of each reference are not taught for the same specific purpose. For example, compounds of Biewenga are directed to thiol-containing free radical scavengers whereas the compounds of Yeadon are directed to effectors of glutathione metabolism. As a skilled artisan can attest to, the pharmacology of the two agents are different, at

least with regard to the treatment of COPD. The cited teachings of the Biewenga and Yeadon, even at the broadest interpretation, do not teach or suggest a combination comprising these two agents. Absent hindsight, nothing in the teachings of any of the cited references would guide or sufficiently motivate a skilled artisan to reformulate the references to use the claimed composition in a manner and/or form taught by the instant invention.

Unexpected effects

In the Kerkhoven case, "it was determined that the claims require no more than mixing of the two conventional detergent compositions" and that "the appellant had not demonstrated any unexpected advantage for the claimed process." The Office Action alleges that "there is no evidence in the record establishing the Applicant's combination of agents is any more effective or in any way different than any single member of the combination." Again, this statement is incorrect. The instant specification explicitly teaches to a skilled worker that the claimed invention involves much more than mere mixing of the two compounds and that the claimed combination leads to "unexpected results." To this end, the Examiner is cordially requested to review the disclosure contained in Tables 6 and 7 and the analysis thereof provided in Examples 4 and 5.

For example, in Example 4 of the instant specification, an unexpected effect of a combination of α-lipoic acid and silibilin on the cellular thiol status of alveolar macrophages is disclosed. It is taught therein that "With the addition of the monosubstances α-lipoic acid or silibinin, no modulation of the cellular thiol expression was to be observed. In contrast, with the combination of α-lipoic acid and silibinin, a clear rise in cellular thiol expression could be demonstrated, starting after 24 hours, which reached a superadditive and significant maximum over the entire test period in the presence of 70 µg/ml silibinin. (emphasis added)." Similarly, in the *ex vivo* phagocytosis assay (i.e., Example 5), it was demonstrated that "the induction of phagocytosis with the combination of α-lipoic acid and silibinin in a concentration of 70 µg/ml was similar [to the one afforded by a combination of α-lipoic and ambroxol]. Here, too, a significant improvement in the capacity for phagocytosis was demonstrated, parallel to a restoration of the thiol status (emphasis added).

Therefore, in view of the forgoing arguments and remarks, it is respectfully submitted that the instantly claimed subject matter is fully inventive over the cited references and that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness. As such, all the rejections under 35 U.S.C. §103(a) must be withdrawn.

Withdrawal of all the rejections and passage to allowance is cordially requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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